

AWARD NUMBER: W81XWH-15-1-0273

TITLE: The Association between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

PRINCIPAL INVESTIGATOR: Andrea Burnett-Hartman, PhD, MPH

CONTRACTING ORGANIZATION: Kaiser Foundation Research Institute
Portland, OR 97227

REPORT DATE: August 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE August 2017		2. REPORT TYPE Annual		3. DATES COVERED 1 Aug 2016 - 31 July 2017	
4. TITLE AND SUBTITLE The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-15-1-0273	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Andrea Burnett-Hartman Email: Andrea.N.Burnett-Hartman@kp.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Kaiser Foundation Research Institute 1800 Harrison St. 16 th Floor Oakland, CA 94612-3429				8. PERFORMING ORGANIZATION REPORT	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The objective of this study is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated colorectal polyps (SSPs). The project's specific aims are as follows: 1) Estimate the risk of colorectal cancer or advanced polyps in patients who have SSPs with cytological dysplasia compared to patients with SSPs that lack cytological dysplasia; and 2) Evaluate if the risk of incident colorectal cancer or advanced polyps varies according to methylation markers in SSPs. The following progress was made during years 1 & 2: Human Subjects approval was obtained from all institutions, SSPs with subsequent colorectal neoplasia and interval cancers were identified, the pathology review form and protocol were finalized, assays for methylation markers were optimized, tissue slide and block pulling and the standard pathology reviews were completed, data cleaning of the pathology review data was finished and analyses of these data begun, tissue sectioning was completed on 85% of samples, and DNA extraction was completed on 60% of samples. Also, Dr. Burnett-Hartman participated in regular career development opportunities, including attending clinical research seminars, presenting at national and local research meetings, and continued to connect with new clinical partners at Kaiser Permanente Colorado. Dr. Burnett-Hartman also maintained regular meetings with mentors and collaborators at the Fred Hutchinson Cancer Research Center, the University of Washington, and Kaiser's Institute for Health Research.					
15. SUBJECT TERMS Colorectal Cancer, Colorectal Polyps, Sessile Serrated Polyps, Methylation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	UU	26	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	8
5. Changes/Problems.....	9
6. Products.....	9
7. Participants & Other Collaborating Organizations.....	9
8. Special Reporting Requirements.....	10
9. Appendix I: Pathology Review Form.....	12
10. Appendix II: Research Support: Burnett-Hartman.....	13
11. Appendix III: Research Support: Grady.....	17
12. Appendix IV: Research Support: Upton.....	23

1. INTRODUCTION:

Recent research suggests that in addition to advanced conventional adenomas, some other polyp pathologies, such as sessile serrated polyps (SSPs), may be important precursors for colorectal cancer. Previously, SSPs were thought to have no malignant potential, but cross-sectional studies of molecular markers have linked SSPs to a subset of colorectal cancers characterized by a CpG Island methylator phenotype (CIMP) and methylation of key DNA repair genes, such as *MLH1* and *MGMT*. However, it is not clear which SSP features are associated with an increased risk of colorectal cancer. Thus, the primary objective of this study is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with SSPs. We hypothesize that patients with SSPs that exhibit cytological dysplasia, *MLH1* or *MGMT* methylation, or patients that have CIMP-high SSPs will have an increased risk of incident colorectal cancer and metachronous advanced colorectal polyps compared to patients with SSPs that lack these characteristics. To test this hypothesis, we identified a cohort of patients who were diagnosed with SSPs at the University of Washington Medical Center during an index colonoscopy between 2003 and 2013. Within this cohort, we will select 100 patients with SSPs who later developed colorectal cancer or advanced polyps and 200 patients with SSPs who did not develop colorectal cancer or advanced polyps after their SSP diagnosis. For these 300 study participants, we are in the process of conducting a standardized pathology review to assess the presence of cytological dysplasia in the index SSPs and molecular testing of index SSPs for CIMP and methylation of specific candidate genes. We will use logistic regression models to compare the risk of colorectal cancer and advanced colorectal polyps in those with each biomarker to those without each biomarker. We will also estimate the sensitivity and specificity of each biomarker to predict the risk of subsequent colorectal cancer or advanced polyps. Research findings from this study will improve effectiveness of colorectal cancer screening tests by informing the development of evidence-based guidelines for the surveillance of patients with SSPs.

2. KEYWORDS:

Colorectal cancer, colorectal polyps, molecular markers, DNA methylation, sessile serrated polyps, screening

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Below is a table displaying the major goals and milestones for this project in accordance with the approved scope of work. Target completion dates, actual completion dates, and percent complete are also listed. Dr. Burnett-Hartman has continued to make progress towards accomplishing the primary study aims in Year 2. She also participated in all planned career development activities during the first 2 years of this award. Note, the table below shows goals and milestones for the entire project period, including goals and milestones that are planned for Year 3.

Table. Major Goals and Milestones

	Target Completion Date	Actual Completion Date	Percent Complete	Notes
Study Set up				
Update local IRB and obtain approval	11/1/15	10/23/2015	100%	IRB approval was obtained through UW, Fred Hutch and KPCO.
Complete IACUC/ HRPO/ACURO applications and obtain approvals	1/1/16	2/12/16	100%	

Complete study protocol for tissue pulling/sectioning and pathology review	12/1/15	9/1/15	100%	We completed the protocol/form quickly, so that we could include the form in our human subjects applications.
Specific Aim 1: Estimate the risk of incident colorectal cancer or metachronous advanced polyps in patients who have SSPs with cytological dysplasia compared to patients with SSPs that lack cytological dysplasia.				
Pulling clinical polyp tissue slides and tissue blocks on 300 patients	4/1/16	2/1/17	100%	We originally planned to pull all slides and blocks at once. However, Northwest Biotrust worked with Dr. Upton to pull batches as Dr. Upton reviews them.
Standard Pathology review of 300 patients	7/1/16	4/1/17	100%	Dr. Upton begun pathology review later than expected due to changes in her office space; she has now completed path review.
Data cleaning of pathology data	9/1/16	6/1/17	100%	
Complete data analysis of pathology data using STATA and summarize data in tables, figures, and graphs	2/1/17		10%	Completion of pathology review was delayed due to changes in the pathologist work space and schedule; analysis of path review data expected 10/1/17.
Preparation, submission, and presentation of abstract on pathology data for national meeting	8/1/17		0%	Dr. Burnett-Hartman will submit an abstract for the National Digestive Disease Week meeting on December 1, 2017.
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18		0%	
Specific Aim 2: Evaluate whether the risk of incident colorectal cancer or advanced neoplasia varies according to certain methylation markers in SSPs, including the presence of CIMP, methylated <i>MLH1</i>, <i>MGMT</i> or <i>BMP3</i>.				

Tissue sectioning	9/1/16		85%	This activity was delayed, because path review needs to be complete before tissue sectioning; new target date is 9/1/17.
Polyp tissue DNA extraction and quantification for 300 samples	12/1/16		60%	Samples are being extracted as sectioning is complete for each batch; new target date 11/1/17
Methylite PCR Assay for 300 Samples, including quality control procedures (i.e. <i>ALU</i> control and 5% blind replication sample)	8/1/17		5%	Although testing of study samples has not begun, we have optimized the assay for 6 out of the 11 DNA methylation markers in preparation for testing study samples.
Data cleaning of CIMP and candidate gene methylation data	9/1/17		0%	
Complete data analysis of methylation data using STATA and summarize data in tables, figures, and graphs	12/1/17		0%	
Preparation and submission, and presentation of abstract for national meeting	5/1/18		0%	
Manuscript preparation, co-author review, submission of manuscript for publication, and responding to journal reviewer comments	7/31/18		0%	
Additional Career Development Activities				
One-on-one meetings with mentors and collaborators	Throughout project period		N/A	Dr. Burnett-Hartman has had mentor meetings throughout Year 2 (see additional information under career development activities).
Attend and present at University of Washington Medical Center, Fred Hutchinson Cancer Research Center, and Kaiser Permanente clinical research seminars	Throughout project period		N/A	Dr. Burnett-Hartman has attended and presented at clinical research meetings (See additional information under career development activities).
Attend the American Society for Clinical Oncology GI Symposium and workshops	3/1/17	2/1/18	0%	The ASCO GI meeting is in January 2018; Dr. Burnett-Hartman will attend this meeting.

Attend and present study findings at Digestive Disease Week (The annual meeting of the American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, Society of the Surgeons of the Alimentary Tract, and American Association for the Study of Liver Diseases)	7/1/18		0%	
--	--------	--	----	--

What was accomplished under these goals?

As detailed in the table above, during years 1 & 2, we accomplished the following goals/objectives:

1. Institutional Review Board Human Subjects review and approval through the University of Washington, Fred Hutchinson Cancer Research Center, and Kaiser Permanente Colorado.
2. Completed IACUC/ HRPO/ACURO applications and obtain approvals
3. Developed the standard pathology review form (see attached appendix)
4. Selected the final list of methylation markers to analyze in our colorectal polyp samples
5. Optimized the methylation assay for DNA methylation markers
6. Completed tissue slide and block pulling
7. Completed standard pathology review
8. Completed data cleaning for path review data and began analysis of path review data
9. Began tissue sectioning and DNA extraction

The following goals/objectives, had planned completion dates during year 2. However, due to an unanticipated delay in beginning pathology review as a result of renovations in the study pathologist's work space and changed work schedules for histopathology, the following are currently behind schedule:

1. Completing data analysis of the pathology review data
2. Completing tissue sectioning (needed to be done after pathology review is complete)
3. Polyp tissue DNA extraction and quantification

These activities will be completed in the first quarter of year 3.

What opportunities for training and professional development has the project provided?

1. **Training in clinical cancer research through seminars** – During Years 1 and 2 of this award, I attended multiple clinical research seminars, including: Translational Research in Oncology Seminars (quarterly through Kaiser Permanente), Center for Effectiveness and Safety Research Seminars (monthly through Kaiser Permanente), Genomics Workgroup Seminars (monthly through Kaiser Permanente), and Translational Research in Colorectal Cancer Seminars (monthly through the Fred Hutchinson Cancer Research Center).
2. **Meetings with mentorship team** – I have maintained a strong mentorship team and meet with one or more of my mentors via phone, video conference, or in-person on a weekly basis. In these meetings, we discuss ongoing projects, future grant applications, study design, and analyses methods. My mentors include Drs. Grady, Newcomb, and Zheng from the Fred Hutchinson Cancer Research Center, Dr. Inadomi from the University of Washington, and Dr. Feigelson from Kaiser Permanente Colorado's Institute for Health Research.
3. **Protected time for clinical research and developing new collaborations with clinical researchers** – As planned, I have maintained 30% protected time for this award and over 60% time devoted to other successfully funded clinical research projects (see attached Research Support Document). Kaiser also provides institutional support to allow for future project development and grant proposal development. This year, I collaborated on 2 new successfully funded grant applications using institutional support. These include an NIH-funded project on Lynch Syndrome and a Garfield foundation-funded project on precision medicine. I also worked

on 3 additional grant applications, 1 of which was not funded; the other 2 received competitive scores and are pending final review by the National Cancer Institute. I have maintained connections with new potential collaborators in clinical cancer research, including Dr. Mark Powis in Kaiser Gastroenterology and Dr. Alex Mentor in Kaiser Oncology, and established a new connection to Dr. Scott Kono in Kaiser Oncology. I also now serve on the KP Colorado Colorectal Cancer Quality Council.

4. Attendance at national meetings – In Year 1, I attended the following National Clinical Research Meetings: Center for Safety and Effectiveness Research (Denver, CO, October 2015), American Society of Preventive Oncology (Columbus, OH, March 2016), and Health Care Systems Research Network (Atlanta, GA, April 2016). In Year 2, I attended and presented at: The American Association for Cancer Research Colorectal Cancer Symposium (Tampa, FL, September 2016), American Society for Preventive Oncology (Seattle, WA, March 2017), and Health Care Systems Research Network (San Diego, CA, March 2017).

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, my study team and I will accomplish the following major goals/objectives:

1. Complete analysis of the pathology review data to determine the association between nuclear dysplasia in sessile serrated polyps and colorectal cancer and advance colorectal polyp risk (Aim 1)
2. Submit an abstract of our findings on nuclear dysplasia in sessile serrated polyps for presentation at a national clinical research meeting
3. Complete tissue sectioning and DNA extraction on all sessile serrated polyps included in this project
4. Complete DNA methylation assays on all polyp tissue DNA samples
5. Clean and analyze the DNA methylation data
6. Develop a manuscript summarizing the results of Aims 1 and 2
7. Continue to pursue career development activities, including: meetings with mentors, attending clinical research seminars, developing new clinical research proposals, and attending and presenting research findings at national clinical research meetings

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report in this period, but future results may impact the DNA markers that are used in stool-based DNA testing for colorectal cancer screening.

What was the impact on society beyond science and technology?

Nothing to report in this period, but future results may inform the surveillance for colorectal cancer in patients with specific types of sessile serrated polyps and ultimately improve the effectiveness of colorectal cancer screening.

5. **CHANGES/PROBLEMS:**

Nothing to report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Publications, conference papers, and presentations

Nothing to report.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

We are in the process of collecting tissue biospecimens; future results from this project may inform colorectal cancer surveillance guidelines for patients with sessile serrated polyps, improve the effectiveness of colorectal cancer screening, and identify new DNA markers to include in stool-based DNA tests.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

What individuals have worked on the project?

Name:	<i>Andrea Burnett-Hartman</i>
Project Role:	<i>Principle Investigator</i>
Researcher Identifier	ANDREABH
Nearest person month worked:	3.60
Contribution to Project:	<i>Dr. Burnett-Hartman is the PI of this project and is responsible for the overall scientific and administrative management for this project, including: compliance with human subjects policies, study design, protocol development, analysis, interpretation, and dissemination of research results.</i>
Funding Support:	No additional funding was provided

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes, please see attached other support document for Dr. Burnett-Hartman, her mentor, Dr. Grady, and study pathologist, Dr. Upton.

What other organizations were involved as partners?

We have two subcontracts under this award. Our partners are Fred Hutchinson Cancer Center and the University of Washington.

- **Organization 1 Name:** Fred Hutchinson Cancer Research Center
 - **Location of Organization:** 1100 Fairview Ave. N., Seattle, WA 98109
 - **Partner's contribution to the project:** Development and optimization of the methylation specific PCR assays that will be used to assess the polyp DNA is in progress. DNA extractions are ongoing at the Fred Hutchinson Cancer Research Center and methylation analysis will be completed in Year 3. Also, Dr. Grady is serving as a mentor to Dr. Burnett-Hartman under this award, and they meet regularly to discuss project progress and career development opportunities. Dr. Burnett-Hartman also attends Dr. Grady's monthly seminars in Translational Research in Colorectal Cancer.
 - **Financial support:** Years 1 & 2 total funds committed \$71,776; \$28,408 spent; \$43,368 remaining balance will be used in Year 3 to complete DNA extraction and methylation analysis.
 - **In-kind support:** N/A
 - **Facilities:** The Fred Hutchinson Cancer Research Center has state-of-the-art laboratories for conducting medical research. The labs encompass a total of 35,000 square feet and include, private lab space, common shared equipment rooms, shared resource space (for genotyping and other molecular work, pathology/histology, and specimen processing), and offices and conference facilities for faculty and staff. The molecular testing for this project will be completed in the Grady Lab at the Fred Hutchinson Cancer Research Center.
 - **Collaboration:** Dr. Burnett-Hartman worked closely with Dr. William Grady on study design, selection of the relevant methylation markers, and assay development in Years 1 and 2. Dr. Grady also actively mentors Dr. Burnett-Hartman.
 - **Personnel exchanges:** N/A
- **Organization 2 Name:** University of Washington
 - **Location of Organization:** 1959 NE Pacific St., Box 357470, Seattle, Washington
 - **Partner's contribution to the project:** Dr. Upton served as Co-Investigator on this project and worked on the pathology-related aspects of the project, including a standard pathology review for people with clinically diagnosed sessile serrated polyps.
 - **Financial support:** Years 1 & 2 total funds committed \$35,388; \$35,388 spent; \$0 remaining balance.
 - **In-kind support:** N/A
 - **Facilities:** For diagnostic and research purposes, the University of Washington's Department of Pathology stores and keeps inventory of H&E slides and associated formalin-fixed paraffin-embedded tumor blocks on patients who had biopsies and/or resections performed at the University of Washington Medical Center and Harborview Medical Center. Northwest Biotrust at the University of Washington has the infrastructure to efficiently pull H&E slides and tumor blocks for clinical and research purposes. This project uses Northwest Biotrust to pull relevant tissues slides and blocks; Dr. Upton, anatomic pathologists at the University of Washington reviews these slides and blocks in a designated office equipped with a high-powered digital microscope.
 - **Collaboration** Dr. Burnett-Hartman has worked closely with Dr. Melissa Upton to develop the pathology review form and is in the process of reviewing index H&E slides to confirm the sessile serrated polyp diagnosis and characterize nuclear dysplasia within the polyp tissue samples.
 - **Personnel exchanges** N/A

8. SPECIAL REPORTING REQUIREMENTS

N/A

9. APPENDICES:

Appendix I: Pathology Review Form

Appendix II: Research Support for Dr. Burnett-Hartman

Appendix III: Research Support for Dr. Grady

Appendix IV: Research Support for Dr. Upton

APPENDIX I - STANDARD PATHOLOGY REVIEW FORM

Date of Pathologist Review ____ / ____ / ____	STUDY ID: _____
DATA ENTRY Date: ____ / ____ / ____ Initials: ____	DATA QC Date: ____ / ____ / ____ Initials: ____

	Comments:
Materials for Review: Slides (#) Box #	

10=polyp(s) NOS 11=hp1=goblet cell hp 12=hp2=microvesicular hp 13=adenoma NOS 14=tubular adenoma 15=tubulovillous adenoma	16=villous adenoma 17=P-J polyp 18=juvenile/inflammatory polyp 19=other polyp 20=sessile serrated polyp 21=indeterminate for HP vs SSP	22=traditional serrated adenoma (TSA) 23=mixed polyp HP/AD 24=mixed polyp SSP/AD 25=mixed polyp SSP/TSA 26=mixed polyp TSA/AD 27=prolapse polyp	30=Carcinoma in situ 40=Invasive CRC 90=normal 91=inconclusive (cannot tell if normal or lesional) 93=benign 99=other
--	---	--	--

Slide	Code (see above) & Confidence (0-100)		Comments	% Lesional	Tangential Orientation	Nuclear Dysplasia	Abnormal Crypts	
							#	%
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		
	__ __				<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes-LGD <input type="checkbox"/> Yes-HGD <input type="checkbox"/> No		

APPENDIX II: EXISTING/PENDING/PREVIOUS SUPPORT – BURNETT-HARTMAN

BURNETT-HARTMAN, ANDREA N.

EXISTING SUPPORT (As of 08/09/2017)

R01 CA 168338 (Newcomb) NIH/CA A Cohort Study of Sessile Serrated Polyps and Subsequent Colorectal Neoplasia	04/22/13 – 3/31/18	0.90 CM
--	--------------------	---------

Recent evidence implicates an additional group of polyps, sessile serrated polyps (SSPs), as important precursors to colorectal cancer. This project will investigate the clinical significance of SSPs in colorectal neoplasia, with the long-term goal of characterizing new high risk-groups to improve the effectiveness of colorectal cancer screening.

Contracting Officer: Ester Young, National Cancer Institute, Office of Grants Administration, BG 9609 9609 Medical Center Drive, Rockville, MD 20892-9760

NIH U01CA163304 (Co-PIs: Feng/Barlow) NIH/NCI PROSPR Statistical Coordinating Center (PSCC)	09/20/11 – 08/31/17	0.10 CM
---	---------------------	---------

The goal of the PROSPR Statistical Coordinating Center (PPSCC) is to coordinate the research of PROSPR Research Centers (PRCs) to achieve PROSPR's mission of evaluating and improving the cancer screening process (recruitment, screening, diagnosis, and referral for treatment).

Contracting Officer: Tonya Parker, National Cancer Institute, Office of Grants Administration, BG 9609 RM 3E346, 9609 Medical Center Drive, West Tower, Rockville, MD 20805

ADM000369 Kaiser Permanente of Colorado Institutional Support- Institute for Health Research	Ongoing N/A	0.24 CM
--	----------------	---------

The institutional funding provides salary support for investigators within the Institute for Health Research.

Contracting Officer: Kasier Foundation Health Plan of Colorado, 10350 E. Dakota Ave., Denver, CO 80231

RNG000511 (Feigelson) Kaiser Foundation Program Office Kaiser National Biobank	01/15/17 – 12/31/17	1.60 CM
--	---------------------	---------

The KP National Biobank is a collaboration across all Kaiser regions nationally funded by Kaiser Permanente Program Office. The goal of the KP National Biobank is to collect blood samples from 500,000 adults KP members and utilize them, combined with survey data and medical information to create a state of the art resources for genetic and health services research.

Contracting Officer: Kaiser Permanente Program Office, 1800 Harrison St. 16th Floor, Oakland, CA 94612-3433

(This Award) W81XWH-15-1-0273 (Burnett-Hartman) DOD/CDMRP The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk	08/01/15 – 08/31/18	3.60 CM
---	---------------------	---------

The primary objective of this career development award is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated polyps.

Contracting Officer: Elayne Seiler, Grants Specialist, USA MED Research MAT CMD, 1077 Patchel Street, BLDG 1077, Fort Detrick, MD 21702

U24CA171524 (Kushi) 09/25/15 – 8/31/18 (NCE) 0.24 CM
NIH/NCI
Cancer Research Network: a Research Resource within Health Care Delivery System

The goal of this grant is to take advantage of the HMO Research Network, a consortium of nonprofits HOMs, to study issues related to cancer prevention, detection and control.

Contracting Officer: Teresa Parker, Grants Management Officer, Office of Grants Administration, BG 9609
RM 3E346, 9609 Medical Center Drive, West Tower, Rockville, MD 20805

R01 CA179906 (Newcomb) 05/01/17 – 04/30/18 0.60 CM
NIH/NCI
Serrated Colorectal Cancer: An emerging Disease Subtype

The objective of this project is to characterize factors relating to the genetic predisposition, clinical presentation, and prognosis of serrated colorectal cancer.

Contract Officer: National Cancer Institute, Office of Grants Administration, BG 9609
9609 Medical Center Drive, Rockville, MD 20892-9760

CDRN-1306-04681 (McGlynn) 10/01/16 – 9/30/17 0.42 CM
PCORI
Pilot Feasibility study of Molecular Tumor Marker Testing in Colorectal Cancer Tissue Samples from PORTAL

In order to conduct research to characterize the molecular markers in colorectal tumors, researchers must be able to access clinical tissue blocks, isolated DNA from these tissue blocks, and successfully test this DNA for important tumor markers, such as BRAF mutation and CpG Island Methylator Phenotype (CIMP). In this pilot study, we will test the feasibility of conducting studies aimed at molecular characterization of colorectal cancers within the PORTAL CRC cohort.

Contracting Officer: Scott Solomon, Director of Contracts Management and Administration, 1828 L Street NW, Suite 900, Washington, DC 20036

CDRN-1306-04681 (McGlynn) 04/01/17 – 10/6/2018 1.00 CM
PCORI
PORTAL 2: Colorectal Cancer Cohort

The objective of this project is to build a cohort of newly diagnosed colorectal cancer cases across 6 health care systems and to conduct colorectal cancer research aimed at improving outcomes for colorectal cancer patients.

Contracting Officer: Scott Solomon, Director of Contracts Management and Administration, 1828 L Street NW, Suite 900, Washington, DC 20036

PAR-13-055 8/1/17 – 7/31/22 1.20 CM
National Institute of Health
Implementing Universal Lynch Syndrome Screening across Multiple HealthCare Systems: Identifying Strategies to Facilitate and Maintain Programs in Different Organizational Contexts

This project seeks to identify strategies that are important to implementing and sustaining Universal Lynch Syndrome screening programs in different healthcare systems and moves health systems towards implementing tailored prevention strategies.
Contracting Officer: Pending

RNG209101 (Aziz) 2/15/17 – 12/31/17 2.10 CM
Garfield Memorial Foundation
Kaiser Permanente Medicine Assessment and Response
The primary objectives of this project are to identify attitudes, barriers, and facilitators to returning research-derived genomic information among KP members and enable the development of robust, stakeholder-informed return of research-derived genomic testing results policies and procedures.
Contracting Officer: Edward Thomas, Director, Garfield Memorial Fund, One Kaiser Plaza, Oakland, CA 94612

PENDING

N/A 8/1/17 – 10/30/2018 1.08 CM Medial
Early Sign
Implementing a CRC Risk Prediction Algorithm to Increase CRC screening in those identified as High Risk.

This project aims to test the performance of an EMR-based algorithm to detect colorectal cancer in KPCO members ages 50-75 years old who are not up-to-date with colorectal cancer screening.
Contracting Office: Pending

PFA-CA-16-017 12/1/17 – 11/30/22 0.90 CM
National Cancer Institute
Coordinating Center for Population-based to Optimize Cancer Screening (PROSPR) (U24)

The goal of the PROSPR Coordinating Center (PCC) is to coordinate the research of PROSPR Research Centers (PRCs) to achieve PROSPR's mission of evaluating and improving the cancer screening process (recruitment, screening, diagnosis, and referral for treatment).
Contracting Officer: Pending

RFA-CA-16-016 12/1/17 – 11/30/22 3.60 CM
NCI
PROSPR II Lung

The long-term goal of this multi-site center grant is to identify critical gaps in the lung cancer screening process and to design innovative, multilevel interventions to reduce lung cancer mortality, particularly among underserved populations.
Contracting Officer: Pending

PREVIOUS SUPPORT

R03 CA186215 (Burnett-Hartman) 04/04/14 – 03/31/17 0.96 CM
NCI
Using Medical Informatics to Follow-up a Colorectal Sessile Serrated Polyp Cohort

The primary objective of this proposal is to gather preliminary data to estimate the risk of colorectal cancer in a large cohort of patients with clinically diagnosed sessile serrated polyps.
Contracting Officer: Ester Young, National Cancer Institute, Office of Grants Administration, 9606 Medical Center Drive, Bethesda, MD 20892-9760

KL2 TR000421 (Disis) 06/01/12 – 01/05/15 9.00 CM
NIH/NCATS
Institute of Translation Health Sciences (KL2)

This is a training award for Dr. Burnett-Hartman from the University of Washington's Institute of Translational Health Sciences.
Contracting Officer: Todd Wilson, National Center for Advancing Translational Sciences, BG 1DEM RM 914, 6701 Democracy Boulevard, Bethesda, MD 20817

R01 CA097325 (Newcomb) 05/17/04 – 04/30/10 6.00 CM
NIH/NCI
Colon Cancer Pathways: Hyperplastic Polyps & Adenomas

To investigate the relationship between risk factors, epigenetic characteristics and polyps, we propose to conduct a population based case-control study of hyperplastic polyps, adenomatous polyps, and normal controls. This study will provide the largest study of risk factors for hyperplastic polyps, their genetic characterization, and comparisons to adenomas and normals. The results of this study will have implications for understanding the biology and prevention of colorectal cancer.
Contracting Officer: Barbara Fisher, National Cancer Institute, Office of Grants Administration 9609 Medical Center Drive, West Tower, 2nd Floor, Rockville, MD 20850

R03 CA137752 (Newcomb) 08/01/09 – 07/31/12 3.00 CM
NIH/NCI
Human Papillomavirus Association with Subsets of Colorectal Cancer

The overall goal of this project is to conduct a case-control study of localized colorectal cancer to determine the association between high-risk HPV infection and tumor and personal characteristics.
Contracting Officer: Amy Connolly, National Cancer Institute, Office of Grants Administration 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850

R03 CA153323 (Newcomb) 08/01/10 – 07/31/13 3.00 CM
NIH/NCI
GWAS Identified Colorectal Cancer SNPs and Colorectal Polyp Risk

This project, an ancillary study to R01 CA097325, seeks determine the risk of adenomas and hyperplastic polyps associated with 10 specific polymorphisms identified through GWAS, and the genes or regions of the genome that house these loci using a tagSNP approach.
Contracting Officer: Barbara Fisher, National Cancer Institute, Office of Grants Administration 9609 Medical Center Drive, West Tower, 2nd floor, Rockville MD 20850

OVERLAP

There is no scientific or budgetary overlap. If the Pending projects are funded, Dr. Burnett-Hartman anticipates reducing effort on the following studies:

CDRN-1306-04681 (McGlynn) is due to end 10/6/2017 available effort 0.42 CM

U24CA171524 (Kushi) reduction of 0.84 CM

RNG209101 (Aziz) reductions of 1.20 CM

R01 CA168338 (Newcomb) reduction of 0.64 CM

APPENDIX III: EXISTING/PENDING/PREVIOUS SUPPORT – GRADY

GRADY, WILLIAM M.

EXISTING SUPPORT

Institutional Funds (Grady) required	02/01/07 - ongoing	Effort: not
University of Washington Rodger C. Haggitt Endowed Chair in Gastroenterology Research Donation (Grady) required	variable 09/01/14 - 08/31/17	Effort: not
Mercer Island Rotary These funds support biomarker research in the Grady lab. Award Administrator: Nural Booth, norgun@fredhutch.org. Restricted donation (Grady) required	09/01/14 - 10/31/17	Effort: not
Cottrell T These funds support research in the Grady lab. Award Administrator: Angela Bush, abush@fredhutch.org. Institutional Support (Grady) required	05/01/13 - 04/30/18	Effort: not
FHCRC / Listwin Family Foundation Early Detection of Colon Cancer Research These funds support biomarker research in the Grady lab. Award Administrator: Angela Bush, Manager, Benefactor Relations; abush@fhcrc.org.		
Institutional Support (Grady) FHCRC ColoCare Study The objectives of this study are to identify factors that determine both short-term and long-term survival in a prospective cohort of colorectal cancer patients. Award Administrator: Doug Lowe, MS, MBA, Division Fiscal Administrator, Clinical Research Division; dlowe@fredhutch.org .	07/01/14 - 06/30/15	effort: not required
2P30CA015704-40 (Gilliland) NIH NCI Cancer Center Support Grant The Fred Hutchinson/University of Washington Cancer Consortium (Consortium) brings together more than 450 members with research interests in basic, clinical, and public health sciences related to cancer. The goal of the Consortium is the elimination of cancer through more effective prevention, diagnostics, and treatment, deriving from fundamental insights into the biology of the disease. The extensive interdisciplinary collaboration among the partner institutions in the cancer research disciplines of basic, clinical, and public health sciences affords new opportunities to reduce suffering and mortality from cancer. The Consortium faculty are organized into 16 productive research programs with the emphasis on the Public Health (Biostatistics, Epidemiology, Prevention), Clinical (Transplantation Biology, Clinical Transplantation, Human Immunogenetics, Immunology, Infectious Disease), Fundamental Sciences (Basic, Human Biology), and programs that impact all three disciplines (Breast, Prostate, Gynecologic, Genetics, Imaging, and Genetic Instability). Dr. Grady serves as head of the Gastroenterology Program. Grants Management Specialist: Gerard B. McCann; mccannge@mail.nih.gov .	01/01/97 - 12/31/19	1.2 CM
Pilot Project (Grady, Grim)	12/15/15- 12/14/17	0.12 CM
Development of Intestinal Organoids Culture Systems to Study the Pathogenesis of Colorectal Cancer		

Specific aims: Aim 1.) Establish colon organoid cultures from primary mouse and human colon epithelium; Aim 2.) Perform genome editing using CRISPR/Cas9 on immortalized human colon epithelial cells to introduce CRC relevant gene mutations; Aim 3.) Use CRISPR/Cas9 genome editing in colon organoid cultures to introduce CRC relevant gene mutations into primary colon cells.

Grants Management Specialist: Gerard B. McCann; mccannge@mail.nih.gov.

1R01CA194663-01 (Grady)

04/14/15 - 03/31/19

1.2 CM

NIH NCI

(PQC1) Accelerated Biological Aging and Colon Polyp to Cancer Progression

Specific aims: 1.) To determine if the biological age of the normal colon mucosa predicts the presence of advanced colon adenomas or adenocarcinomas; 2.) To determine if age-related DNA methylation is increased in biologically older colons and correlates with the presence of advanced adenomas or CRC; 3.) To determine if tumorigenic effects of age related senescence mediate the increased risk of polyp→CRC transformation.

Grants Management Specialist: Samantha Ann Farrell; samanthal.farrell@mail.nih.gov.

1R01CA189184-01A1 (Li, Ulrich)

05/01/15 - 04/30/20

0.19 CM

NIH NCI

Discovery and Verification of Novel Biomarkers of Colorectal Cancer Recurrence

This study is specifically designed to meet the overarching goal of discovery and verification of novel blood-based biomarkers predictive of recurrence among CRC patients, through achieving the following specific aims: 1.) Discovery and verification of novel biomarkers predictive of recurrence among CRC patients; and 2.) Discovery and verification of novel biomarkers useful for the early detection of CRC recurrence.

CA140616 (Burnett-Hartman)

08/01/15 - 07/31/18

0.24 CM

DoD/CDMRP (Prime: Kaiser Permanente of Colorado)

The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

The primary objective of this career development award is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated polyps.

Contracting Officer: Elayne Seiler, Grants Specialist, USA MED Research MAT CMD, 1077 Patchel Street, BLDG 1077, Fort Detrick, MD 21702

DeGregorio Family Foundation (Grady)

03/01/16 - 02/28/18

0.12 CM

DeGregorio Family Foundation

Epigenetic Drift in Barrett's Esophagus as a Novel Risk Marker for Esophageal Adenocarcinoma

This study will determine whether recently identified epigenetic "biological clock" biomarkers can be used to more precisely 'date' the age of BE tissue and refine current EAC risk estimates based on multiscale modeling, which can improve our understanding of the pathogenesis of EAC and ability to detect EAC at an early stage.

Award Administrator: Angela Bush, Manager, Benefactor Relations; abush@fhcrc.org.

2U01CA152756 (Grady, Markowitz)

05/13/2016- 03/31/21

1.2 CM

NIH NCI (EDRN prime)

Biomarkers for Reducing Mortality of Cancers of the Colon and Esophagus

The goal of this EDRN renewal proposal is the discovery and validation of i) biomarkers of increased risk of gastrointestinal cancers, and ii) biomarkers for the early detection of gastrointestinal malignancies. We particularly target cancers of the colon, that are the second leading cause of cancer deaths in the U.S., and adenocarcinomas of the esophagus, that are the fastest increasing cause of cancer deaths, with a 7-fold increased incidence over the last 3 decades, and with a 90% lethality rate.

Suzanne Morris, Department Administrator, Case Gastrointestinal Cancers SPORE, and Cancer Research Laboratory of Dr. Sanford Markowitz, Case Comprehensive Cancer Center , [216-368-1976](tel:216-368-1976),

STTR- Team Grant 07/01/2016-06/30/18 0.24 CM
FHCRC/various

Development of Simultaneous Multiple Interaction T-cell Engaging (SMITE) Antibodies for the Treatment of Colorectal Cancer

We propose to develop novel BiTE derivatives that will activate T-cell signaling to overcome this resistance

mechanism, enhancing the potency of BiTE antibodies, and to apply these to the treatment of CRC.

Award Administrator: Rachel Galbraith, Program Administrator, Solid Tumor TransRes, 206-667-5183, rgalbrai@fredhutch.org

STTR – Program Infrastructure Grant 07/01/2016-06/30/2018 0.12 CM
FHCRC/various

STTR CRC Team Grant

We propose to generate and characterize CRC PDX tumors that can then be used in studies of novel therapeutics and studies of the molecular and cell biology of CRC.

Award Administrator: Rachel Galbraith, Program Administrator, Solid Tumor TransRes, 206-667-5183, rgalbrai@fredhutch.org

Edge Pilot Program (Grady) 4/01/17-03/31/18 0.12 CM
Edge/UW

Pilot studies of the effects of dietary factors on the colon epigenome using human “miniguts”

These studies will provide new insights in the field of nutri-epigenomics, and may lead to CRC prevention strategies that have not been recognized to date.

Award Administrator: Elizabeth Guzy, EDGE Center Manager, 206 685-5333, eguzy@uw.edu

R21 CA209203 (McTiernan) 4/1/2017 – 3/31/2019 0.6 CM
NIH

Exercise Effects in Men & Women on Colon DNA Methylation

This project will investigate the effects of physical activity on colon DNA methylation in genes related to colon cancer. Excessive DNA methylation is thought to be a risk factor for colon cancer, and no previous study has tested the effect of exercise on DNA methylation in the colon. The project includes 202 initially sedentary men and women who have already completed the trial from which colon samples will be used.

Award administrator: Sarah M. Lee, Grants Management specialist, 240-276-6280, SARAH.LEE@nih.gov

5U54CA163060 (Chak, Grady, Markowitz) 04/01/2017-03/31/22 1.2 CM
NIH/NCI (CWRU prime)

Genetic Determinants of Barrett’s Esophagus and Esophageal Adenocarcinoma

In the proposed studies, we will identify and evaluate detection biomarkers for Barrett’s esophagus, a precancerous condition for EAC. The detection biomarkers can be used in non-invasive assays for detecting people who have Barrett’s esophagus. These people can then be placed in surveillance programs in order to

prevent them from getting EAC.

Award Administrator: Alicia DePlatchett, Department Administrator, alicia.deplatchett@case.edu.

PENDING

PQ6R01R01CA220004 (Grady) 07/01/17-06/30/22 1.2 CM NIH/
University of Wisconsin

Radiogenomics of colorectal polyps to assess benign proliferative vs. premalignant states.

This project will have the potential to identify factors that affect the progression of polyps to CRC and will provide insight into the idea that some polyps may be “born to be bad” rather than “being born good and becoming bad over time”. Program Official: Matthew Young, 240-276-9790, youngma@mail.nih.gov

1 R01 CA223520-01 (Grady, INADOMI, Luebeck) 09/01/17-08/31/22 1.2 CM

NCI/NIH

Impact of Tissue Age on Colorectal Cancer Risk and Prevention

Our primary hypothesis is that biological tissue age provides a more reliable predictor of CRC risk than chronological age, and may be used to improve discrimination between low- and high-risk individuals.

Program Official: Susan Scott, 240-276-6951, scotts2@mail.nih.gov

U01CA215857 (Luebeck, Grady, Newcomb, Hazelton)

04/01/18-03/31/23

1.8 CM

NIH/NCI

Multiscale Study of Tissue Aging, Field Cancerization, and Colorectal Screening

This project will integrate information across a wide range of temporal and spatial scales using multiscale modeling; develop hierarchical models of cancer that bridge from the molecular scale to CRC incidence and mortality in the population; and make significant progress towards a systems biology aided clinical trial design that evaluates the impact of targeted screening of individuals at high risk of CRC progression.

Program Official: Susan Scott, 240-276-6951, scotts2@mail.nih.gov

PREVIOUS SUPPORT

5U01CA152756-05 (Grady, Markowitz)

08/25/10 - 06/30/16

1.8 calendar
(concurrent)

NIH NCI

3U01CA152756-05S1

Identify and Validate Novel Epigenetic Molecular Markers for Colorectal Neoplasm

We propose to create a Research Team to lead an EDNR Biomarker Developmental Lab to discover novel methylated genes using cutting-edge and complementary approaches, HumanMethylation27 DNA Analysis Beadchip (Illumina Infinium platform), and deep sequencing of captured NaHSO₃ treated DNA (Agilent and Solexa). The specific aims are: 1.) To develop and validate epigenetic signatures of colon adenomas and early stage non-metastatic colon cancers; 2.) To perform a comprehensive epigenomic characterization of colorectal cancer molecular subtypes (stages I-III, n=1536); 3.) To identify and characterize biologically relevant novel methylation targets in colorectal cancer.

5U54CA163060-05 (Chak, Grady, Markowitz, Shaheen)

NIH NCI

09/26/11 - 08/31/16

CWRU (prime)

Genetic Determinants of Barrett's Esophagus and Esophageal Adenocarcinoma

The overall objectives of this BETRNet Translational Research Center (TRC-F) are: 1.) to conduct a rigorous, integrated spectrum of transdisciplinary human research in Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC); 2.) to increase the biological understanding of key observations made by our clinical researchers (familial aggregation of BE and EAC, restitution of squamous mucosa after ablation); 3.) to translate knowledge derived from genetic and physiologic research to solving clinical dilemmas in detection, prognosis, and therapy of BE in order to prevent EAC and improve the outcomes of EAC; 4.) to foster a transdisciplinary and translational research culture and to effectively expand and enhance scientific research focused on BE and EAC; 5.) to evaluate research and transdisciplinary programs and to continuously improve research, productivity and enhance translational implementation.

Sub-project i.d. # 5418 (Grady, PL)

1.2 calendar **

Project 2: The Biology and Translation of Epigenetic Alterations in Barrett's Esophagus (concurrent)

Specific Aims: 1.) To characterize the genome wide methylation status of BE, BE+LGD, BE+HGD, and EAC and to correlate the methylation status with clinicopathological features of the patients; 2.) To determine the methylome of familial vs. sporadic BE and EAC cases and determine if familial cases differ from sporadic cases based on the methylation status of the BE and EAC; 3.) To determine whether methylated genes can be used as detection molecular markers for the identification of people with BE using Cytosponge esophageal brushings; 4.) To determine if methylated genes can be used for the prediction of recurrent BE in Barretts esophagus patients after Radiofrequency Ablation (RFA).

5U01CA163304-04 (Barlow, Thornquist) 09/19/11 - 08/31/16 effort: 3.8% (0.46 calendar)

NIH NCI effort: not measurable after 1/31/15

PROSPR Statistical Coordinating Center (PSCC)

The goal of the PROSPR Statistical Coordinating Center (PSCC) is to coordinate the research of PROSPR Research Centers (PRCs) to achieve PROSPR's mission of evaluating and improving the cancer screening process (recruitment, screening, diagnosis, and referral for treatment).

Grants Management Specialist: Renee Carruthers; carruthersr@mail.nih.gov.

5U54CA143682-05 (Davies) 09/30/09 - 08/31/14 effort: 5% (0.6 calendar)
NIH NCI / ASU

A Center for the Convergence of Physical Science and Cancer Biology

Core 2 – Materials Core (Grady) (FHCRC subaward)

A center for studying physical characteristics of cancer cells, including nuclear and cytoplasmic membrane elasticity using single cell computed tomography, and chromatin structure using atomic force measurements, will be developed to gain new understandings of the physical properties of cells that may be used to therapeutic or diagnostic advantage.

5P01CA077852-15 (Monnat) 07/01/09 - 06/30/14 effort: 2.5% (0.3 calendar)

NIH NCI

Human RecQ Helicases in Biology and Oncology

Project 5: Human Tumor Analysis (Grady)

The goal of this project is to assess the role of RecQ helicases in colon cancer. The specific aims are: 1.) To determine the frequency of loss of expression and epigenetic inactivation of Rec Q helicases in two of the most common epithelial cancers that occur in the US: colorectal cancer and breast cancer; 2.) To determine the role of WRN, BLM, and RECQL4 inactivation and RECQ helicase interacting proteins in modifying the effect of chemotherapy on colorectal cancers (CRC); 3.) To determine the role of WRN, BLM, and RECQL4 inactivation and RECQ helicase interacting proteins in modulating the effect of chemotherapy on breast cancers (BrCA).

5P30CA015704-38 (Corey) 01/01/09 - 12/31/14

NIH NCI

Cancer Center Support Grant

Pilot Project (Grady) 04/01/11 - 12/31/12 effort: 2% (0.24 calendar) *

Novel Forward Genetic Screen for Functional Colon Cancer Genes: Development of Analysis Techniques

The studies in this project employ an innovative forward genetic screen using the Sleeping Beauty (SB) transposon mouse model to identify novel genes that cooperate with TGFBR2 inactivation to affect CRC formation. This novel mouse model system uses the cre-lox system to direct mutagenesis events to the tissue of interest (e.g. colon) and thus limits confounding events caused by tumors arising in unrelated tissues. In order to identify the novel genes that arise in this system, we will establish a new method for integration site analysis using next generation sequencing (Illumina HiSeq 2000 System, Genomics Shared Resource). The Specific Aim of this proposal is as follows: To develop a high throughput method for identifying novel genes that cooperate with TGF- β signaling inactivation to effect CRC formation in the SB Transposon mouse model, which is a forward genetic screen.

5U24CA074794-14 (Newcomb)
NIH NCI

09/22/08 - 08/31/12

effort: 5% (0.6 calendar)

The Colon Cancer Family Registry: Seattle

The Colon Cancer Family Registry - Seattle (CCFR -S), a center within the multinational six-site Colon CFR consortium, is a population-based resource for studies of the genetics and genetic epidemiology of colorectal cancer. Activities for this period (Phase III) will include: expanding accrual of the cohort, conducting follow-up with existing cohort members, continued biospecimen collection and processing, and provision of data and samples to CCFR-approved research projects.

5R01CA115513-05 (Grady)
calendar)
NIH NCI

01/01/07 - 06/30/12

effort: 18.75% (2.25

TGF-Beta Signaling and Colon Cancer

This research will address how *TGFBR2* and its inactivation paradoxically affect central biological behaviors of cancer, cell proliferation and apoptosis, and will elucidate the signaling pathways and downstream proteins that regulate these events in both *in vitro* and *in vivo* systems. The specific aims are: 1.) To determine the effect of TGF- β signaling pathway inactivation in the setting of Apc mutation and Wnt signaling activation on intestinal cancer formation; 2.) To determine if TGF- β signaling pathway inactivation cooperates with Kras2 mutation and Ras-Raf pathway activation in intestinal cancer formation; 3.) To determine the *in vivo* consequences of TGFBR2 inactivation on colon cancer initiation and progression using novel mouse models of intestinal cancer that genetically recapitulate human colon cancer, Apc1638N;LSL-Kras2G12D;Tgfr2IEKO, and Apc1638N;LSL-Trp53R172H;Tgfr2IEKO mice.

CRA (Grady)
calendar) Takeda Pharmaceuticals North America, Inc
(no-cost extension)

07/01/08 - 06/30/12

effort: 2% (0.24

Epigenetic Alterations in Barrett's Epithelium and Esophageal Adenocarcinoma

The specific aims of this grant are: 1.) To identify novel methylated loci involved in the initiation and progression of Barrett's esophagus through the use of genome-wide methylation studies using "methylation" arrays; and 2.) To identify a panel of methylated genes that discriminates BE, BE+HGD, and EAC and to determine the potential of these genes to be used as predictive biomarkers for BE progression.

OVERLAP

None

APPENDIX IV: EXISTING/PENDING/PREVIOUS SUPPORT – UPTON

UPTON, MELISSA P.

EXISTING SUPPORT

W81XWH-15-1-0273 (Burnett-Hartman)

08/01/15 – 07/31/18

DOD/CDMRP

0.24 CM

The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk

The primary objective of this career development award is to identify histologic characteristics and molecular markers associated with an increased risk of colorectal cancer in patients with sessile serrated polyps.

Contracting Officer: Elayne Seiler, Grants Specialist, USA MED Research MAT CMD, 1077 Patchel Street, BLDG 1077, Fort Detrick, MD 21702

FFPE Validation of a Survival Gene Signature in HPV-Negative Oral Cavity Cancer

12/1/2014 – 12/31/2017

NIH/NCI (1 R01 CA177736-01A1) Chen, Chu, PI

0.6 calendar

Project Description: Oral cancer is a substantial global health burden, with an estimated 529,000 new cases and 292,000 deaths occurred in 2012. The results of this study have the potential to create, for the first time, a rapid, reliable, and cost-effective formalin-fixed, paraffin-embedded tumor based assay to improve the prediction of survival of human papillomavirus-negative oral cavity cancer patients and help physicians and patients to make timely, personalized treatment choices.

Role: Co-Investigator

Sponsor Contact: Chu Chen, PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:M5-C800, PO Box 19024, Seattle, WA 98109-1024, cchen@fhcrc.org.

PENDING:

None

PREVIOUS SUPPORT

Needle biopsy preservation and preparation for rapid 3D pathology of pancreas 8/14/2014 – 8/31/16

NIH (1 R21 CA186791-01) Seibel, Eric PI

0.36 calendar

Project Description: The goal of this project is to reduce the time for biopsy tissue preparation to less than half the standard time in a pathology lab. Furthermore the 3D architecture of the tissue will be preserved for the first opto-mechanical measures of biopsy intactness. The diagnostic value of the needle biopsy specimens after automated preparation will be determined by experienced pathologists. The ability to visualize 3D morphology within tissue biopsies will also allow the pathologists to better compare ex vivo diagnosis with new in vivo 3D imaging technologies, such as confocal, optical coherence tomography, and photoacoustic imaging. This project is expected to lead to a transformation in pathology from 2D to 3D, and in the ability to provide less invasive, low-cost and rapid cancer diagnosis, directly affecting several millions of US citizens per year.

Role: Co-Investigator

Sponsor Contact: Eric Seibel, PhD., Human Photonics Laboratory, University of Washington, Box 352600, Seattle, WA 98195, eseibel@uw.edu.

Esophageal Cancer from Cells to Population: A Multiscale Approach 9/1/2013 – 6/30/2016

NCI/FHCRC (Sub-award# 0000813441) Inadomi, John 0.48 calendar

Project Description: The goal of the proposed research is to reduce the burden of esophageal adenocarcinoma (EAC) by optimizing surveillance of patients with Barrett's esophagus (BE) using cutting-edge endoscopic imaging and advanced epigenetic profiling of neoplastic tissues in combination with standard endoscopic techniques

Role: Co-Investigator

Sponsor Contact: John Inadomi, PhD., Division of Gastroenterology, University of Washington, Box 356424, Seattle, WA 98195, jinadomi@medicine.washington.edu.

Colon Cancer Biomarkers 8/16/2010 – 6/30/2015

FHCRC (Sub-award# 0000748868) Lampe, Paul, PI 0.12 calendar

Project Description: Affinity based strategies to fast track development of colon cancer biomarkers. The proposed research involves the discovery of early detection and diagnostic biomarkers of colon cancer using high density antibody microarrays as part of the Early Detection Research Network.

Role: Co-Investigator

Sponsor Contact: Paul Lampe PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:M5-C800, PO Box 19024, Seattle, WA 98109-1024, plampe@fhcrc.org.

GI Service Center 7/1/2012 – 6/30/2015

University of Washington 1.20 calendar

Project Description: Dr. Upton serves as the GI Pathology Medical Director.

Integrated Genomic Approach for Therapeutic Target Selection in Oral Cancer 1/1/2014 – 12/31/2014

FHCRC (Sub-award#0000764374) Mendez, Eduardo, PI

0.12 calendar

Project Description: The aims for the proposed study are to validate the usefulness of markers by testing the respective markers for invasive cancer, metastasis, and survival of OSCC patients for their predictive abilities for clinical outcomes of OSCC using previously collected but not yet tested tissue samples and data and new samples and data to be collected in year 1 of the proposed study.

Role: Co-Investigator

Sponsor Contact: Eduardo Mendez PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:D5-390, PO Box 19024, Seattle, WA 98109-1024, edmendez@uw.edu.

NIH (5 R01 EB 07636-04) Lin, Lih-yuan, PI

0.34 calendar

Project Description: The objective of this project is to develop and validate a new generation of scanning fiber-optic endoscopes and molecular contrast agents for improving early detection of cancer in luminal organs.

Role: Co-Investigator

Sponsor Contact: Lih-yuan Lin, PhD., M414 EE1 Bldg., 185 Stevens Way, University of Washington, Seattle, WA, 98195-2500, lylin@uw.edu.

Complete 3D Imaging of Needle Biopsy to Diagnose Pancreatic Cancer

3/15/2012 – 2/28/2014

NSF (CBE-1212540) Seibel, Eric PI

0.24 calendar

Project Description: An exploratory project is designed to improve the minimally-invasive diagnostic ability of needle biopsy for pancreatic cancer. To accomplish this, a systems approach begins with thin-needle core biopsy specimens acquired from ex vivo tissues from mouse models of pancreatic cancer and resected human tissue. The visualization of the 3D images with H&E staining and selected immunofluorescence biomarkers will be used to determine the presence of neoplasia and cancer invasion. This OPTM diagnosis by a pathologist will be compared to matching the needle aspirate (FNA) in a blinded study against the gold standard of tissue-slice pathology.

Role: Co-Investigator

Sponsor Contact: Eric Seibel, PhD., Human Photonics Laboratory, University of Washington, Box 352600, Seattle, WA 98195, eseibel@uw.edu.

Oral Cancer: Molecular Profiles and Clinical Outcomes

9/1/2009 – 8/31/2012

NIH (2R01 CA95419) Chen, Chu, PI

0.6 calendar

Project Description: The purpose of this competing renewal is to validate various biomarkers that we have previously found to be associated with tumor characteristics and clinical outcomes of oral squamous cell carcinomas in our previous R01 application

Role: Co-Investigator

Sponsor Contact: Chu Chen, PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., MS:M5-C800, PO Box 19024, Seattle, WA 98109-1024, cchen@fhcrc.org.

TGF-Beta Signaling and Colon Cancer

12/01/2006 – 12/31/2011

NIH (5R01 CA115513) Grady, William, PI

0.12 calendar

Project Description: The major goals of this project are to identify and validate microcytometer-based methylation specific PCR molecular markers assays for assessing the prognosis of colorectal cancer. My role is to assess tissue specimens of colonic and intestinal neoplasms and to provide accurate TNM staging data for use in the interpretation of the molecular marker assay results.

Role: Co-Investigator

Sponsor Contact: William Grady, PhD., Fred Hutchinson Cancer Research Center (FHCRC), 1100 Fairview Avenue N., PO Box 19024, Seattle, WA 98109-1024, wgrady@fhcrc.org.

OVERLAP

None